REMARKS

Claims 15-30 are pending in the present application. Claims 1-14 have been canceled without prejudice or disclaimer.

Claims 15-28 have been amended to delete the term "hydrate" and the term "hydrate of a salt." In addition, claim 15 has been amended at page 2, line 18 to delete "-CH2-OR8" without prejudice or disclaimer to the canceled subject matter. Claims 25-26 have been amended to recite a "therapeutically effective amount," as suggested by the Examiner. Claims 27-30 have been amended to replace the term "illness" with the term "disorder." Support for this amendment is found at page 43, lines 18-21, of the present specification. No new matter has been added.

Applicants thank the Examiner for withdrawing the rejection of claims 15-30 as obvious over US 6,160119 or US 6,197,783 or WO 00/26217 in view of DE 4308095 to Budt et al. (Please note that in the Official Action the Examiner refers to "DE 4308095 to Bundgaard et al." However, the author of DE 4308095 is properly Budt et al.).

In view of the following, further and favorable consideration is respectfully requested.

I. In item 4 at page 2 of the final Official Action, the rejection of claims 25-26 under 35 USC § 112, second paragraph, has been maintained for reasons of record.

The Examiner asserts that claims 25-26 do not recite a "therapeutically effective amount" and that pharmaceutical compositions by definition must be effective yet non-toxic. The Examiner recommends amending claims 25-26 to recite "a therapeutically effective amount."

Pursuant to the Examiners suggestion, claims 25-26 have been amended to recite "a therapeutically effective amount" without prejudice or disclaimer to the amended subject matter merely to speed prosecution of the present application. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

II. In item 5 at page 2 of the final Official Action, the rejection of claims 15-30 under 35 USC § 112, first paragraph, has been maintained for reasons of record.

Claims 15-28 have been amended to delete the terms "hydrate" and "hydrate of a salt" without prejudice or disclaimer to the canceled subject matter. Claims 29 and 30 are dependent on claims 27 and 28, respectively. Accordingly, this rejection is moot.

III. In item 6 at page 3 of the final Official Action, the rejection of claims 15-30 as obvious under 35 USC § 103(a)over Grundler et al. (WO 98/54188) or Simon et al. (WO 98/42707), in view of DE 4308095 to Budt et al., has been maintained for reasons of record.

The Examiner asserts that the instant claims are the prodrug form of hydroxyl. More specifically, the Examiner asserts that it would have been obvious to the skilled artisan to prepare the prodrug of the hydroxyl compound of Grundler et al. or Simon et al. as taught by Budt et al.

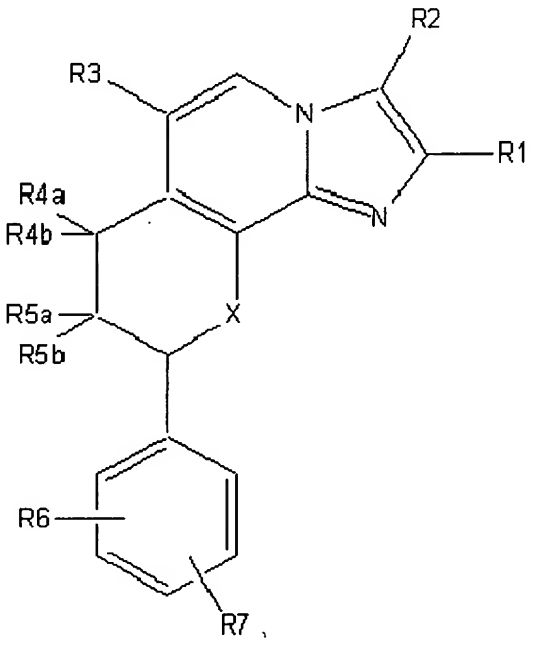
In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d

1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

a. The Presently Claimed Invention

Presently pending independent claim 15 is drawn to a compound of the formula 1,



(1)

in which

R1 is methyl,

R2 is methyl,

R3 is hydrogen,

one of the substituents R4a and R4b is hydrogen and the other is 1-4C-alkoxy or 1-4C-alkoxy-1-4C-alkoxy,

R5a is the radical –OR',

R5b is hydrogen,

R6 is hydrogen,

R7 is hydrogen and

X is O (oxygen) or NH,

and where

R' is selected from the group consisting of

-C(O)-NR8R9,

-C(O)-alk-NR8R9,

-C(O)-alk-C(O)-NR8R9,

-P(O)(OH)2,

-S(O)2NR8R9,

-C(O)-R8,

-C(O)-C6H3R10R11,

-C(O)-OR8,

-C(O)-alk-C(O)-R8,

-C(O)-alk-C(O)-OR8,

-C(O)-C(O)-R8, and

-C(O)-C(O)-OR8,

where

alk is 1-7C-alkylene,

R8 is hydrogen, 1-10C-alkyl or 1-4C-alkyl substituted by halogen, carboxyl, hydroxyl, sulfo (-SO3H), sulfamoyl (-SO2NH2), carbamoyl (-CONH2), 1-4C-alkoxy or 1-4C-alkoxycarbonyl,

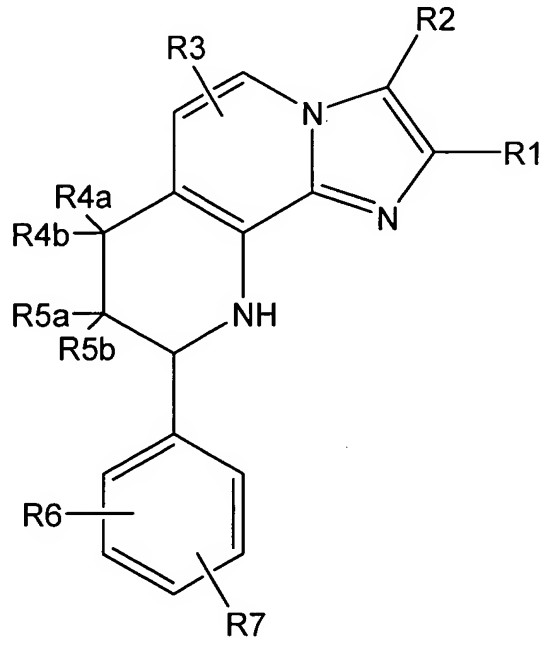
R9 is hydrogen or 1-4C-alkyl,

R10 is hydrogen, halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or trifluoromethyl and

R11 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy.
or a solvate, salt, or solvate of a salt thereof.

b. Simon et al., '707

Simon et al. '707 teaches compounds of the formula



wherein

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl or hydroxyl-1-4C-alkyl,

R3 is hydrogen or halogen,

one of the substituents R4a and R4b is hydrogen and the other is hydrogen, hydroxyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy or 1-4C-alkylcarbonyloxy, or in which R4a and R4b together are O (oxygen),

one of the substituents R5a and R5b is hydrogen and the other is hydrogen, hydroxyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy or 1-4C-alkylcarbonyloxy, or in which R5a and R5b together are O (oxygen),

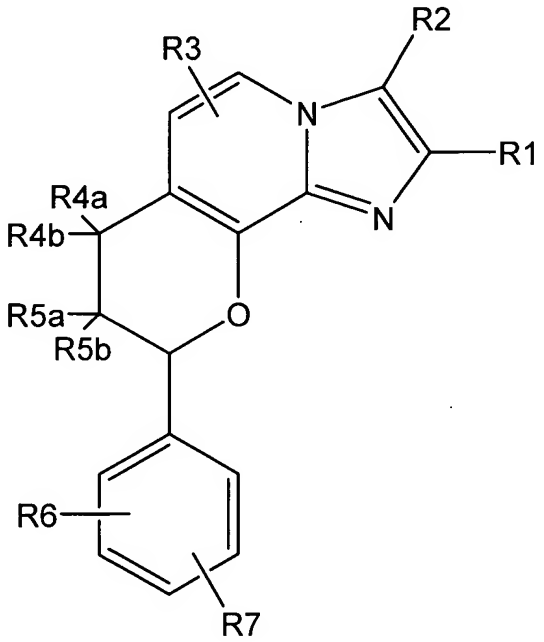
or in which one of the substituents R4a and R4b on the one hand and one of the substituents R5a and R5b on the other hand is in each case hydrogen, and the other substituents in each case together form a methylenedioxy radical (-O-CH2-O-) or an ethylenedioxy radical (-O-CH2-CH2-O-), where R4a, R4b, R5a and R5b are not simultaneously hydrogen,

R6 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or trifluoromethyl and

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy.

c. Grundler et al., '188

Grundler et al. '188 teaches compounds of the formula



wherein

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl or hydroxyl-1-4C-alkyl,

R3 is hydrogen or halogen,

one of the substituents R4a and R4b is hydrogen and the other is hydrogen, hydroxyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy or 1-4C-alkylcarbonyloxy, or in which R4a and R4b together are O (oxygen),

one of the substituents R5a and R5b is hydrogen and the other is hydrogen, hydroxyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy or 1-4C-alkylcarbonyloxy, or in which R5a and R5b together are O (oxygen),where R4a, R4b, R5a and R5b are not simultaneously hydrogen,

or in which one of the substituents R4a and R4b on the one hand and one of the substituents R5a and R5b on the other hand is in each case hydrogen, and the other substituents in each case together form a methylenedioxy radical (-O-CH2-O-) or an ethylenedioxy radical (-O-CH2-CH2-O-),

R6 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or trifluoromethyl and
R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy.

Budt et al. teach general characteristics of prodrugs and in particular, "the best known prodrugs are in fact esters of drugs containing hydroxyl or carboxyl groups." Budt et al. also list in Table 2 examples of ester derivative compounds developed as prodrugs for drugs containing a hydroxyl group. Nowhere does the Budt et al. reference contain any evidence of a suggestion or incentive that would have motivated the skilled artisan to combine its teachings with the teachings of the Simon et al. reference to arrive at the presently claimed invention as required by *In re Fine.*

As discussed in the Response and Amendment filed on April 13, 2006, no teaching can be found in the cited references which would motivate the skilled artisan to pick and choose the particular substituents which make up the presently claimed genus as required by *In re Fine.*

Moreover, Applicants point out to the Examiner that under U.S. patent law, a sub-genus may be separately patentable over a previously disclosed genus.

In further evidence of the non-obviousness of the presently claimed subject matter, submitted herewith is a Declaration under 35 USC § 1.132 by Prof. Dr. Wolfgang Kromer and by Dr. Stefan Potius. Prof. Dr. Kromer and Dr. Potius are joint inventors of PCT

Application No. PCT/EP01/03514, International Publication No. WO 01/72756, for all designated states except CA, CO and the US, whereby the above-identified application is the United States national stage application of PCT Application No. PCT/EP01/03514.

The Declaration provides evidence showing the unexpectedly superior results achieved by the presently claimed compounds as compared to the structurally closest compounds identified as: (i) PC1 (soraprazan, (7R, 8R, 9R)-7-(2-methoxyethoxy)-2, 3-dimethyl-9-phenyl-7, 8, 9, 10-tetrahydroimidazo[1,2-h][1,7]naphtyridin-8-ol); and (ii) PC2 (sorarazan-analogon, (7R, 8R, 9R)-2,3-Dimethyl-8-hydroxy-7-(2-methoxyethoxy)-9-phenyl-7H-8,9-dihydro-pyrano-[2,3-c]imidazo[1,2-a]pyridine).

PC1 falls within the scope of the generic compounds described in Simon et al. '707. PC1 is exemplified in Example 5A of US Pat. No. 6,436,953 to Senn-Bilfinger which corresponds to WO 00/017200. US Pat. No. 6,436,953 to Senn-Bilfinger does not constitute prior art against the present application. PC1 was selected for comparison with the present compounds because it is the structurally closest compound where X=NH to the presently claimed compounds. This is because the present compounds have one R4a or R4b substituent which is a 1-4C-alkoxy or a 1-4C-alkoxy-1-4C-alkoxy as opposed to the compounds expressly described in Simon et al. '707 where one of R4a or R4b is hydroxyl or where these two substituents together are oxygen.

PC2 falls within the scope of the generic compounds described in Grundler et al. '188 which corresponds to WO 01/072755. PC2 is exemplified in Example 1 of US Pat. No. 6,936,623 to Senn-Bilfinger et al. US Pat. No. 6,936,623 to Senn-Bilfinger et al. does not constitute prior art against the present application. PC2 is the structurally closest compound where X=O to the presently claimed compounds because the present

compounds have one R4a or R4b substituent which is a 1-4C-alkoxy or a 1-4C-alkoxy-1-4C-alkoxy as opposed to the compounds expressly described in Grundler et al., '188 where one of R4a or R4b is hydroxyl or where these two substituents together are oxygen.

PC1 and PC2 were prepared and compared with compounds 20 and 48-53 that were prepared in accordance with the method described in the present application and which compounds fall within the scope of present claim 1.

In PC1, R1 and R2 are each CH3 (1-4C-alkyl); one of R4a and R4b is hydrogen and the other is –O-CH2-CH2-OCH3 (1-4C-alkoxy-1-4C-alkoxy); one of R5a and R5b is hydrogen and the other is hydroxyl; and R3, R6, and R7, are each hydrogen.

Likewise, in PC2, R1 and R2 are each CH3 (1-4C-alkyl); one of R4a and R4b is hydrogen and the other is –O-CH2-CH2-OCH3 (1-4C-alkoxy-1-4C-alkoxy); one of R5a and R5b is hydrogen and the other is hydroxyl; and R3, R6, and R7, are each hydrogen.

As can be seen from the Declaration, administration of compounds 20 and 48-53 according to the present pending claims which include the "prodrug" residue noted by the Examiner, for example, –C(O)-R8 with R8 = 1-4 C-alkyl substituted by 1-4C-alkoxy or –C(O)-alk-NR8R9, in the R5 position, results in an increase of AUC of at least 20 % as compared to the AUC levels observed after administration of PC1 and PC2 that were each substituted with only a hydroxyl group in the R5 position. *See* Table 2 of the Declaration. This finding is unexpected and unforeseeable.

The Declaration data clearly establishes that compounds 20 and 48-53 according to the presently pending claims exhibit unexpectedly superior efficacy as compared to the efficacy of the structurally closest compounds PC1 and PC2.

In addition, the data in Table 3 of the Declaration shows that each of the presently claimed compounds 1-6, 8-12, 15-17, 19-20, 28, 30, 32, 34, 36, 38, 39, 43-45, and 47, described on pages 27-37 of the specification, inhibits acid secretion *in vivo* by more than 50 %. This data evidences the high antisecretory potency of the presently claimed compounds substituted with a wide chemical range of residues resulting in different chemical structures.

In view of the foregoing, it is submitted that claims 15-30 are patentable over the applied references. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. In items 7 and 8 at pages 3 and 4 of the final Official Action, the rejection of claims 15-30 under the doctrine of obviousness-type double patenting, has been maintained for reasons of record.

The Examiner asserts that the instant claims wherein R5 is the radical –OR' wherein R' is –CH2-OR8 corresponds to the prior art R5 which is a 1-4C-alkoxy-1-4C-alkoxy.

Claim 15 has been amended to delete the recitation that R' is –CH2-OR8 without prejudice or disclaimer to the canceled subject matter. Claims 16-30 are directly or indirectly dependent on independent claim 15. Accordingly, this rejection is moot.

IV. In item 9 at page 4 of the final Official Action, claims 27-30 have been rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement.

The Examiner asserts that the "specification lacks description of the claim i.e. 'gastrointestinal illness.' ...in the specification there is not description of gastrointestinal illness, which is broader term than gastrointestinal disease." The Examiner concludes the specification describes gastrointestinal disease not gastrointestinal illness and therefore the specification lacks written description for the term "gastrointestinal illness."

Claims 27-30 have been amended to replace the term "illness" with the term "disorder" which term is of equivalent or broader scope than the term "illness." Support for this amendment appears in the specification at page 43, lines 18-21, which states: "...the compounds of formula 1...where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine."

In view of the foregoing, it is submitted that claims 27-30 fully comply with the written description requirement of 35 USC § 112, first paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

V. In item 10 at page 5 of the final Official Action, claims 27-30 have been rejected under 35 USC § 112, first paragraph, as containing new matter.

The Examiner asserts that the term "gastrointestinal illness" constitutes new matter.

As discussed above, Claims 27-30 have been amended to replace the term "illness" with the term "disorder" which term is of equivalent or broader scope than the term "illness." Again, support for this amendment is found in the present specification at page 43, lines 18-21.

In view of the foregoing, it is submitted that claims 27-30 fully comply with the requirements of 35 USC § 112, first paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VI. In item 11 at page 5 of the final Official Action, claim 15 has been rejected under 35 USC § 102(e) as anticipated by Senn-Bilfinger et al., '119.

The Examiner asserts that Senn-Bilfinger et al., '119, teaches the instant claimed compound wherein R5 is a 1-4C-alkoxy-1-4C-alkoxy which corresponds to present claim 15 where R5a is the radical –OR' wherein R' is –CH2-OR8.

Claim 15 has been amended to delete the recitation that R' is –CH2-OR8 without prejudice or disclaimer to the canceled subject matter. Accordingly, this rejection is moot.

VII. In item 12 at page 6 of the final Official Action, claim 15 has been rejected under 35 USC § 102(e) as anticipated by Senn-Bilfinger et al., '783.

The Examiner asserts that Senn-Bilfinger et al., '783, teaches the instant claimed compound wherein R5 is a 1-4C-alkoxy-1-4C-alkoxy which corresponds to present claim 15 where R5a is the radical –OR' wherein R' is –CH2-OR8.

Claim 15 has been amended to delete the recitation that R' is –CH2-OR8 without prejudice or disclaimer to the canceled subject matter. Accordingly, this rejection is moot.

VIII. In item 13 at page 6 of the final Official Action, claim 15 has been rejected under 35 USC § 102(b) as anticipated by Senn-Bilfinger et al., '188.

The Examiner asserts that Senn-Bilfinger et al., '188, teaches the instant claimed compound wherein R5 is a 1-4C-alkoxy-1-4C-alkoxy which corresponds to present claim 15 where R5a is the radical –OR' wherein R' is –CH2-OR8.

Claim 15 has been amended to delete the recitation that R' is –CH2-OR8 without prejudice or disclaimer to the canceled subject matter. Accordingly, this rejection is moot.

IX. In item 14 at page 6 of the final Official Action, claim 15 has been rejected under 35 USC § 102(b) as anticipated by Senn-Bilfinger et al., '707.

The Examiner asserts that Senn-Bilfinger et al., '707, teaches the instant claimed compound wherein R5 is (-O-CH2-O-) which corresponds to present claim 15 where R5a is the radical –OR' wherein R' is –CH2-OR8.

Claim 15 has been amended to delete the recitation that R' is –CH2-OR8 without prejudice or disclaimer to the canceled subject matter. Accordingly, this rejection is moot.

X. In item 15 at page 7 of the final Official Action, claim 15 has been rejected under 35 USC § 102(b) as anticipated by Senn-Bilfinger et al., '217.

The Examiner asserts that Senn-Bilfinger et al., '217, teaches the instant claimed compound wherein R5 is a 1-4C-alkoxy-1-4C-alkoxy which corresponds to present claim 15 where R5a is the radical –OR' wherein R' is –CH2-OR8.

As presented in the Response and Amendment filed on April 13, 2006, Applicants again assert that this rejection is improper since the '217 application is ***not*** prior art against the instant application. *See* MPEP § 706.02(f)(1) III.

In particular, applicants point out that this reference ***cannot*** be considered prior art against the present application under 35 USC §102(e). The Examiner has misapplied the law because the '217 application is an ***international application*** that has an international filing date that is ***prior to November 29, 2000.*** As such, ***it does not have a 102(e) date*** and is ***only*** available under 35 USC § 103(a) or § 103(b) as of its publication date of ***May 11, 2000*** which date is ***after*** Applicants priority date of March 29, 2000.

In view of the foregoing, the Examiner is ***specifically requested*** to acknowledge that Senn-Bilfinger et al., '217, does not constitute prior art against the present application, and thus remove the present rejection.

Assuming *arguendo* Senn-Bilfinger et al., '217 constitutes prior art against the present claims, Senn-Bilfinger et al., '217 does not teach each and every element of the claimed invention as required for anticipation under 35 USC § 102.

Specifically, Senn-Bilfinger et al., '217 teaches compound of formula I where "one of the substituents R4a and R4b has to be R4' and/or one of the substituents R5a and R5b has to be R5'." Substituents R4' and R5' are thio-substituted radicals which are not encompassed by the present claims.

In view of the remarks set forth herein, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

It is submitted that the presently claimed subject matter is novel and patentably distinguishable over the prior art of record. Favorable action with an early allowance of pending claims 15-30 is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments.

In the event that this paper is not timely filed, Applicants hereby petition for an appropriate extension of time. Please charge any such extension of time fee, any fee deficiency or credit any overpayment to deposit account no. 14-0112.

Respectfully submitted,
NATH & ASSOCIATES PLLC

Gary M. Nath
Reg. No. 26,965
Joshua B. Goldberg
Reg. No. 44,126
Susanne M. Hopkins
Reg. No. 33,247
Customer No. 34375

Date: September 1, 2006
NATH & ASSOCIATES PLLC
112 South West Street
Alexandria, VA 22314
Tel: (703) 548-6284
Fax: (703) 683-8396

JBG/SMH\RFOA.doc